4 Peptide Emergence, Evolution and Selection on the Primitive Earth
I. Convergent Formation of N-Carbamoyl Amino Acids Rather than Free α-Amino Acids?

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Abstract After summaizing current knowledge about the origins of primitive Earth organic matter, we focus our attention solely on α-amino acids and their derivatives. We then analyze the mechanism for the formation of these compounds, under both extraterrestrial and primitive-Earth conditions, and show that a “multicomponent system” consisting of prebiotic molecules (hydrogen cyanide, several carbonyl compounds, ammonia, alkyl amines, carbonic anhydride, sodium bicarbonate, borate, cyanic acid) may have been the precursors of these essential compounds. We show that this multi-component system leads reversibly to several intermediate nitriles, which irreversibly evolve, first to α-amino acids and N-carbamoyl amino acids via selective catalytic processes, and then to N-carbamoyl amino acids alone.

4.1 Introduction

The Earth is 4.6 billion years old (4.6 Gyr). Two million years after it was formed, it had attained 80% of its present-day mass, the continents and oceans were already present, the plate-tectonic process had already begun (Martin 1986, 1987; Maas and McCulloch 1991; Carlson 1996; Vervoort et al. 1996; Mojzsis et al. 2001; Wilde et al. 2001), and there was also an atmosphere, though admittedly little is known about it (Selsis 2000). The last 20 per cent of the Earth’s mass (1.2 × 10^{21} tons) was added by meteorites, micrometeorites and comets between −4.4 and −4.1 Gyr (Maurette 2001). The emergence of life may possibly have taken place in this period (acceptedly before −3.5 Gyr); as a consequence its substrate, namely organic matter, was obviously of both exogenous and endogenous origins. Qualitatively and quantitatively assessing each of these two different origins is a question of current importance that we examine, limiting ourselves to amino acids.

Investigation of the chemical mechanisms involved in the formation of both exogenous and endogenous amino acids should eventually provide information on the prebiotic environment. Such research needs first to acquire knowledge on meteoritic amino acids and related compounds (Sects. 4.2 and 4.3) and on the chemical reactions responsible for their synthesis (Sects. 4.4 and 4.5), in order to find out their potential prebiotic relevance (Sect. 4.6) as well as physical constraints on parent bodies (exogenous synthesis).
We conclude by studying a series of reactions that could have led to the formation of peptides, under prebiotic conditions.

4.2 Organic Molecules on the Primitive Earth

An exhaustive inventory of the origins of all the organic molecules occurring on the primitive Earth 4Gyr ago was carried out by Chyba and Sagan (1992). They distinguished three probable sources:

– Exogenous contribution from meteorites, micrometeorites, interplanetary dust particles (IDP), comets, etc.
– Endogenous synthesis associated with impact of such bodies
– Endogenous production associated with other available energy sources (solar UV, lightning, radioactivity, etc.)

The total contribution of these three sources would have been heavily dependent on the composition of the primitive atmosphere. It would, in fact, have ranged from \( \approx 10^{11} \text{kg y}^{-1} \) for a reductive atmosphere to \( \approx 10^{8} \text{kg y}^{-1} \) for a slightly reductive atmosphere (atmospheric \([\text{H}_2]/[\text{CO}_2]\) ratio \( \approx 0.1 \) or less for even lower hydrogen levels. The presence of methane (\( \text{CH}_4 \)) in the primitive atmosphere would have oriented endogenous syntheses towards a considerable production of nitriles, especially the simplest of these, hydrocyanic acid HCN, which amount could have reached ca. \( 10^{10} \text{kg y}^{-1} \). Assuming the volume of the primitive oceans to have been identical to that of the present day, considering only the soluble part of the organic matter (\( \approx 40\% \) of the total determined by Chyba and Sagan (1992), see Cronin and Chang 1993), and supposing this organic matter to be rather stable under its supposed conditions, the primitive oceans could have contained (at a steady state) between ca. \( 0.4 \times 10^{-3} \text{gL}^{-1} \) of total organic matter in the case of a neutral atmosphere and \( 0.4\text{gL}^{-1} \) in the case of a reductive atmosphere. Given the imprecision of current knowledge about the composition of the primitive atmosphere, three different eventualities can be considered:

– A highly reductive atmosphere in which syntheses due to impacts would have predominated over endogenous production due to electrical discharges and solar UV
– A slightly reductive atmosphere in which, by contrast, endogenous syntheses (solar UV, lightning) would have predominated, augmented by the contribution of organic matter from IDPs
– A very slightly reductive, or nonreductive atmosphere in which the contribution of organic matter from IDPs would have predominated

We shall now examine the qualitative aspects linked to these eventualities.
4.3 Exogenous Amino Acids and Related Compounds

Analysis of the organic matter contained in meteorites, especially carbonaceous chondrites, regularly collected on Earth’s surface (Cronin and Chang 1993; Maurette 1998), has provided an approach to extraterrestrial organic chemistry (the study of dense clouds is another possible approach, doubtless more direct, but restricted mostly to volatile materials). This organic matter could correspond to that formed in the early Solar System, or even in the pre-Solar System (Cronin and Pizzarello 1983; Cronin and Chang 1993; Cooper and Cronin 1995; Cooper et al. 2001). It is mainly (> 60%) macromolecular, insoluble and difficult to characterise. The soluble part (< 40%) is a complex mixture of molecular organic compounds in which the following have been characterized: acids (carboxylic, dicarboxylic, hydroxyl, sulfonic, phosphonic); amines; amides; nitrogenous heterocycles including purines and pyrimidines; alcohols; sugars; carbonyl compounds; aliphatic and aromatic hydrocarbons; amino acids and hydantoins. Structures of compounds dealt with in this chapter are shown in Fig. 4.1.

Fig. 4.1. General structure of amino acids and related compounds. All proteinic $\alpha$-amino acids have the L configuration (blue)

4.3.1 Exhaustive Survey of Exogenous Amino Acids

More than 70 different amino acids have been characterized, principally in the Murchison and Murray meteorites (both being carbonaceous chondrites) (Tables 4.1–4.4), representing a total abundance of 75 $\mu$g per g of meteorite. Over a set of 7 other carbonaceous chondrites, the average mass of extracted amino acids was only 0.6 $\mu$g per g. It should, nevertheless, be noted that the mass of organic molecules present in chondrites decreases as a function of the time the materials have spent on the Earth (Cronin and Pizzarello 1983), thus probably leading to an underassessment of the amount of exogenous organic matter. Thus, even if the value obtained for the Murchison meteorite is representative of chondrites and if this value is doubled to take into account the existence of amino acid precursors in the total carbonaceous matter (Cronin and Pizzarello 1983; Cooper and Cronin 1995), the abundance of meteoritic amino acids remains quantitatively low, even considering that chondritic micrometeorites could have...
Table 4.1. The 20 protein α-amino acids: names, 3-letter and 1-letter codes, and numbers of C atoms in their alkyl chains. blue: α-amino acids detected in carbonaceous chondrites

<table>
<thead>
<tr>
<th>Name</th>
<th>3-lett code</th>
<th>1-lett. code</th>
<th># C atoms</th>
<th>Name</th>
<th>3-lett code</th>
<th>1-lett. code</th>
<th># C atoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alanine</td>
<td>Ala</td>
<td>A</td>
<td>3</td>
<td>Leucine</td>
<td>Leu</td>
<td>L</td>
<td>6</td>
</tr>
<tr>
<td>Arginine</td>
<td>Arg</td>
<td>R</td>
<td>5+1</td>
<td>Lysine</td>
<td>Lys</td>
<td>K</td>
<td>6</td>
</tr>
<tr>
<td>Aspartic Acid</td>
<td>Asp</td>
<td>D</td>
<td>4</td>
<td>Methionine</td>
<td>Met</td>
<td>M</td>
<td>4+1</td>
</tr>
<tr>
<td>Asparagine</td>
<td>Asn</td>
<td>N</td>
<td>4</td>
<td>Phenylalnine</td>
<td>Phe</td>
<td>F</td>
<td>3+6</td>
</tr>
<tr>
<td>Cysteine</td>
<td>Cys</td>
<td>C</td>
<td>3</td>
<td>Proline</td>
<td>Pro</td>
<td>P</td>
<td>5</td>
</tr>
<tr>
<td>Glutamic Acid</td>
<td>Glu</td>
<td>E</td>
<td>5</td>
<td>Serine*</td>
<td>Ser</td>
<td>S</td>
<td>3</td>
</tr>
<tr>
<td>Glutamine</td>
<td>Gln</td>
<td>Q</td>
<td>5</td>
<td>Threonine</td>
<td>Thr</td>
<td>T</td>
<td>4</td>
</tr>
<tr>
<td>Glycine</td>
<td>Gly</td>
<td>G</td>
<td>2</td>
<td>Tryptophane</td>
<td>Trp</td>
<td>W</td>
<td>3+8</td>
</tr>
<tr>
<td>Histidine</td>
<td>His</td>
<td>H</td>
<td>3+3</td>
<td>Tyrosine</td>
<td>Tyr</td>
<td>Y</td>
<td>3+6</td>
</tr>
<tr>
<td>Isoleucine</td>
<td>Ile</td>
<td>I</td>
<td>6</td>
<td>Valine</td>
<td>Val</td>
<td>V</td>
<td>5</td>
</tr>
</tbody>
</table>

* though very often detected, Ser is widely considered as a terrestrial contaminant.

delivered larger amounts of organic matter than meteorites themselves. This low rate of exogenous carbon delivery may nonetheless have been of great qualitative importance (see Sect. 4.3.4) for prebiotic chemistry processes on the primitive Earth.

4.3.2 Formation Mechanisms of Exogenous Amino Acids

Out of more than 70 identified extraterrestrial amino acids (Tables 4.2–4.4), 46 (including 8 diacids) have their amine function in the α-position, 13 in the β-position, 10 in the γ-position and 1 in the δ-position. The formation rate and/or the stability of α-isomers therefore appears favoured in extraterrestrial environments.

4.3.2.1 α-Amino Acids

The formation mechanism of α-amino acids has been the subject of a great deal of attention. In the historic experiment of Miller (1953) α-amino acids and α-hydroxy acids were associated with imino diacids HN(CR₂CO₂H)₂, these three compound classes altogether being considered as the signature of Urey–Miller experiments. Miller (1957) explained the formation of the α-amino acids α-hydroxy acids by the Strecker reaction (4.1), without being able to suggest a mechanism
Table 4.2. Names and structures of α-amino acids detected in carbonaceous chondrites

<table>
<thead>
<tr>
<th>2–5 carbon atoms</th>
<th>6,7 carbon atoms</th>
<th>7 carbon atoms (contd)</th>
</tr>
</thead>
<tbody>
<tr>
<td>glycine</td>
<td>leucine</td>
<td>2-amino-4-methyl caproic acid*</td>
</tr>
<tr>
<td>alanine</td>
<td>isoleucine*</td>
<td>2-amino-4,4-dimethyl valeric acid</td>
</tr>
<tr>
<td>sarcosine</td>
<td>norleucine</td>
<td>2-amino-2-ethyl-valeric acid</td>
</tr>
<tr>
<td>2-amino-butyrinic acid</td>
<td></td>
<td>2-amino-3-ethylvaleric acid</td>
</tr>
<tr>
<td>2-amino isobutyric acid</td>
<td></td>
<td>2-amino-5-methyl caproic acid</td>
</tr>
<tr>
<td>N-methyl-alanine</td>
<td>2-amino-2-ethylbutyric acid</td>
<td>2-amino-3-methyl caproic acid*</td>
</tr>
<tr>
<td>N-ethyl-glycine</td>
<td>pseudoleucine</td>
<td>2-amino-3,4-dimethyl valeric acid*</td>
</tr>
<tr>
<td>valine</td>
<td>cycloleucine</td>
<td>2-amino-2,3,3-trimethyl butyric acid</td>
</tr>
<tr>
<td>proline</td>
<td>2-amino-heptanoic acid</td>
<td>2-amino-2-ethyl-3-methylbutyric acid</td>
</tr>
<tr>
<td>isovaline</td>
<td>2-amino-2,3-dimethyl valeric acid*</td>
<td>2-amino-3,3-dimethyl valeric acid</td>
</tr>
<tr>
<td>norvaline</td>
<td>2-amino-2,4-dimethyl valeric acid</td>
<td>2-amino-2-methyl caproic acid</td>
</tr>
</tbody>
</table>

In blue: protein amino acids (only 8; Ser although very often detected, is widely considered as a terrestrial contaminant). * (names in italic): diastereomer pairs (counted as two compounds; most amino acids are enantiomer pairs and counted as a single compound). Boxed (names in bold): amino acids detected as non racemic in meteorites (1–9% ee of L configuration; the methyl group in place of the α-hydrogen makes them resistant to racemization).
Table 4.3. Names and structures of α-amino diacids detected in carbonaceous chondrites

<table>
<thead>
<tr>
<th>Succinic type</th>
<th>Glutaric type</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>aspartic acid</td>
<td>glutamic acid</td>
<td>2-amino pimelic acid</td>
</tr>
<tr>
<td>2-amino-2-methyl succinic acid</td>
<td>2-amino-2-methyl glutaric acid</td>
<td>2-amino adipic acid</td>
</tr>
<tr>
<td>2-amino-3-methyl succinic acid*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(see notes on Table 4.2)

Table 4.4. Names and structures of non-α-amino diacids detected in carbonaceous chondrites

<table>
<thead>
<tr>
<th>β-amino acids</th>
<th>β- (cont.), γ-amino acids</th>
<th>γ- (cont.), δ-amino acids</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-alanine</td>
<td>3-amino-2-ethyl butyric acid*</td>
<td>4-amino-2-methyl valeric acid*</td>
</tr>
<tr>
<td>3-amino-butyric acid</td>
<td>3-amino-3-methyl valeric acid</td>
<td>4-amino-caproic acid</td>
</tr>
<tr>
<td>3-amino-2-methylproponionic acid</td>
<td>3-amino-2,3-dimethyl butyric acid</td>
<td></td>
</tr>
<tr>
<td>3-amino-2-methyl butyric acid</td>
<td>4-amino-butyric acid</td>
<td></td>
</tr>
<tr>
<td>3-amino-3-methylbutyric acid*</td>
<td>4-amino-2-methylbutyric acid</td>
<td></td>
</tr>
<tr>
<td>3-amino-pivalic acid</td>
<td>4-amino-3-methylbutyric acid</td>
<td></td>
</tr>
<tr>
<td>3-amino-valeric acid</td>
<td>4-amino-valeric acid</td>
<td></td>
</tr>
<tr>
<td>3-amino-2-ethylproponionic acid</td>
<td>4-amino-3-methylvaleric acid*</td>
<td>5-amino valeric acid</td>
</tr>
</tbody>
</table>

(see notes on Table 4.2)
for the imino-diacid formation. He nevertheless intuitively considered these three classes altogether to be also the signature of the Strecker reaction.

![Diagram of Strecker reaction]

The early (and still accepted) hypothesis for meteoritic \(\alpha\)-amino acid synthesis considered the Strecker reaction as the most plausible although only two (\(\alpha\)-hydroxy- and \(\alpha\)-amino acids) out of its three-component signature had been identified in meteorites (Peltzer et al. 1984; Cronin and Chang 1993; Botta et al. 2002). The recent discovery of imino diacids in meteorites (Pizzarello and Cooper 2001) completed this signature and confirmed Miller’s hypothesis of the Strecker reaction for meteoritic \(\alpha\)-amino acid synthesis. A better understanding of chemical mechanisms (see Sect. 4.5.2) explains the formation of imino diacids through Strecker processes.

If meteoritic \(\alpha\)-amino acids actually originated through Strecker reactions, then their precursor carbonyl compounds are easily deduced by applying retrosynthesis to the set of meteoritic amino acids (Tables 4.2 and 4.2). This provides the 35 carbonyl derivatives listed in Table 4.5, where all possible isomers are present. The higher their molecular mass, the lower their abundance (relatively to that of \(\alpha\)-amino acids).

The presence of all the possible isomers of these carbonyl derivatives, some of which being still present in meteorites (Jungclaus et al. 1976), clearly shows that they have previously been synthesized by nonselective processes, possibly photochemical. In the long term, this whole set of carbonyl derivatives is to be taken into consideration in a global kinetic model to explain the presence of exogenous and endogenous \(\alpha\)-amino acids on the primitive Earth.

### 4.3.2.2 Non \(\alpha\)-Amino Acids

The proposed mechanism (Cronin and Chang 1993) (4.2) for the formation of \(\gamma\)-amino acids involves the following initial molecules: \(\alpha\), \(\beta\) unsaturated aldehyde 8 variously substituted, hydrocyanic acid and ammonia. After addition of two HCN molecules, cyanohydrins (\(\alpha\)-hydroxy nitriles) 9 are obtained. After hydration and hydrolysis (Strecker reaction), \(\alpha\)-amino nitriles 10 lead to 11 and 12 (when \(R^1\), \(R^2\), and \(R^3\) are hydrogens, 12 is glutamic acid). The following reaction sequence: cyclization of 12, decarboxylation of 13 and hydrolysis of 14 produces \(\gamma\)-amino acids 15, which might therefore appear as degradation prod-
ucts of α-amino 1,3-diacids 12. If so, this would increase the count of exogenous α-amino acids from 46 to about 54, out of 70.

\[
\begin{align*}
R^1 & \quad R^2 \\
\text{HO} & \quad \text{CN} \\
\text{NH}_2 & \quad \text{H}_2\text{N} \quad \text{CN} \\
\text{H}_2\text{N} & \quad \text{CONH}_2 \\
\text{R}^1 & \quad \text{R}^2 \\
\end{align*}
\]

(4.2)

β-amino acids could have been formed according to (4.3) by addition of ammonia on acrylonitrile 16 (R^1 = R^2 = R^3 = H) or its substituted derivatives (R^1, R^2, R^3 \neq H), followed by hydrolysis of the nitrile function (Cronin and Chang 1993).

\[
\begin{align*}
R^1 & \quad R^2 \\
\text{CN} & \quad \text{NH}_3 \\
\text{H}_2\text{N} & \quad \text{R}^1 \quad \text{R}^2 \\
\text{R}^1 & \quad \text{R}^2 \\
\text{R}^1 & \quad \text{R}^2 \\
\end{align*}
\]

(4.3)

The proposed mechanism (Cronin and Chang 1993) (4.4) for the formation of the unique δ-amino acid 21 detected in the meteorites, is similar to that in (4.3), but starting with cyanobutadiene 19 as the initial substrate. This process involves, together with the above addition reaction, a reduction step on 20.

\[
\begin{align*}
\text{CN} & \quad \text{NH}_3 \\
\text{R}^1 & \quad \text{R}^2 \\
\text{H}_2\text{N} & \quad \text{R}^1 \quad \text{R}^2 \\
\text{R}^1 & \quad \text{R}^2 \\
\end{align*}
\]

(4.4)

The formation of proline 25 can be explained either by the mechanism described by (4.5) (detection of pyrrolidine (saturated 22) in interstellar clouds is consistent with this explanation) (Cronin and Chang 1993), or by cyclization of H2N–CH2–CH2CH2CHO.1

\[
\begin{align*}
\text{H} & \quad \text{CN} \\
\text{H} & \quad \text{H} \\
\text{H} & \quad \text{H} \\
\text{H} & \quad \text{H} \\
\end{align*}
\]

(4.5)

1 Another possible pathway involves cyanohydrins H2N–(CH2)n–CH(CN)–OH, the “Strecker precursors” of ornithine (n = 3) and lysine (n = 4): if present, their intramolecular substitution would lead to proline and pipecolic acid, respectively (both compounds being identified in Murchinson and Murray meteorites, but neither lysine nor ornithine).
Table 4.5. The 35 carbonyl derivatives precursor of meteoritic α-amino acids and α-amino diacids. In blue: compounds bearing a nitrile group

<table>
<thead>
<tr>
<th>#C</th>
<th>Aldehydes</th>
<th>Ketones</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1.png" alt="Aldehyde 1" /></td>
<td><img src="image2.png" alt="Ketone 1" /></td>
</tr>
<tr>
<td>2</td>
<td><img src="image3.png" alt="Aldehyde 2" /></td>
<td><img src="image4.png" alt="Ketone 2" /></td>
</tr>
<tr>
<td>3</td>
<td><img src="image5.png" alt="Aldehyde 3" /></td>
<td><img src="image6.png" alt="Ketone 3" /></td>
</tr>
<tr>
<td>4</td>
<td><img src="image7.png" alt="Aldehyde 4" /></td>
<td><img src="image8.png" alt="Ketone 4" /></td>
</tr>
<tr>
<td>5</td>
<td><img src="image9.png" alt="Aldehyde 5" /></td>
<td><img src="image10.png" alt="Ketone 5" /></td>
</tr>
<tr>
<td>6</td>
<td><img src="image11.png" alt="Aldehyde 6" /></td>
<td><img src="image12.png" alt="Ketone 6" /></td>
</tr>
</tbody>
</table>

4.3.3 Other Meteoritic Compounds Closely Related to Amino Acids

Cooper and Cronin (1995) and subsequently Shimoyama and Ogasawara (2002) identified the compounds shown in Fig. 4.2 in the Murchison and Yamato-791198 meteorites.

Lactames 13 and 14 are intermediates in γ-amino acid formation from α-amino acids (4.2). Compounds 26 to 30 are amide or imide derivatives. Compounds 31 are hydantoin (imidazolidine-2,4-diones) which can result from two pathways (Fig. 4.3):

- Either the reaction of cyanic acid on α-amino acids (formed through the Strecker reaction), followed by cyclization (Cooper and Cronin 1995), in which case hydantoins both substituted and unsubstituted on nitrogen 1 can be formed.
- Or the Bücherer–Bergs reaction (Taillades et al. 1998) via the cyclization of isocyanates 35 (see Sect. 4.5.2). In this case only 1-unsubstituted hydantoins are accessible.

Actually only 1-unsubstituted hydantoins have been identified in meteorites, which rather supports the hypothesis of a Bücherer–Bergs pathway.
4.3.4 Non-Racemic Exogenous α-Amino Acids

(see also Cronin and Reisse Chap. 3, Part II)

Six extraterrestrial α-amino acids (framed structures in Tables 4.2–4.4) extracted from the Murchison and Murray meteorites were found as nonracemic (Cronin and Pizzarello 1997; Pizzarello and Cronin 2000). Their enantiomeric excesses ($\lambda$) are between 1.0 and 9.2%. The presence of a CH$_3$ group in the $\alpha$ position instead of an H, argues for their nonbiological origin, which is confirmed by their D/H and $^{13}$C/$^{12}$C isotopic ratios. This enantiomeric excess could be the re-
result, not of chemoselectivity, but rather of enantioselective photodegradation of the initial racemic mixture in the presolar cloud. This photodegradation could have been caused by circularly polarized UV light. Circularly polarized light, although infrared, has been observed in the Orion cloud, meanwhile the origin of such radiation is the focus of numerous questions (Jorissen and Cerf 2002). This hypothesis of partial photodegradation of racemic mixtures is nonetheless consistent with laboratory results obtained as early as 1977 (Flores et al. 1977). The mechanism of this reaction was recently developed further (Nishino et al. 2001).

The existence of these nonracemic compounds opens up a wide research area in the field of the homochiral synthesis of peptides. They could have induced a symmetry breaking during the production of peptides by a “molecular engine” described in the next chapter of this book.

4.3.5 Exogenous Peptides

It is only recently that the first exogenous peptides were looked for and found in the Murchison and Yamato-791198 meteorites. The authors of these works (Shimoyama and Ogasawara 2002) showed, however, that the only peptides present are glycylglycine (Gly-Gly) and the corresponding diketopiperazine. The abundance of these compounds, (of the order of ca. 20 pmol g\(^{-1}\)), and, above all, the absence of both Ala-Gly and Gly-Ala, despite the presence of Ala and Gly in meteorites, led Shimoyama to conclude that these compounds were probably formed by classical dehydration processes, rather than via the copolymerization of NCA, which should have produced sequential macromolecules (see our next chapter in this book). The potential exogenous imports thus appear to be of minor importance.

4.3.6 Conclusion

α-Amino acids are therefore major compounds of the meteorite amino acid pool, both in structural diversity (54/70) and abundance, including 8 of the 20 protein amino acids\(^2\). Their formation through Strecker reactions is consistent with the presence in meteorites of the three compound classes characteristic of this kind of reaction: α-hydroxy- and α-amino acids, imino diacids. The – yet unexplained – formation of imino diacids is detailed in Sect. 4.5 devoted to chemical studies. Since β- and δ-amino acids are rather marginal, we shall not go into detail of their synthesis in that section, focusing rather on Strecker and Büchner–Bergs processes.

\(^2\) If we include asparagine and glutamine (ω-amide forms of aspartic and glutamic acids, respectively). Though never detected in meteorites, these amino acids were very probably formed, but would have been readily and completely hydrolysed (into aspartic and glutamic acids respectively) during either meteorite ageing or extraction process.
4.4 Endogenous Organic Matter

The endogenous production of organic matter is unknown due to the absence of any fossil record. It must have greatly depended on the environment, especially on how reducing or oxidizing this environment was.

Knowledge of the different sources of available energy and their respective contributions to the endogenous production of organic matter, has evolved over time. While solar UV has always been considered to have played an important quantitative role (Chyba and Sagan 1992) the origin of organic nitrogen chemistry nonetheless still needs to be explained, given the short wavelengths (\(\lambda < 100\,\text{nm}\)) required for the photolysis of \(N_2\) (Selsis et al. 1996; Selsis 2000).

In this area, the (somewhat underestimated) importance of lightning and meteoritic impacts was recently re-evaluated (Navarro-Gonzalez et al. 1998, 2001), together with its consequences on the production of nitric oxide, NO. This aspect will be presented in Commeysras et al., Chap. 5, Part II, for which it is of high importance: a part of so-produced NO, remained in the atmosphere, might have played a fundamental role in the further synthesis of peptides.

Meanwhile, the other part of this NO, dissolved in the primitive ocean, could have been reduced to \(\text{NH}_3\) by \(\text{Fe}^{2+}\) in the ocean, even in the presence of high levels of cyanide (Summers and Chang 1993; Summers and Lerner 1998). The ammonia thus produced could have made a major contribution to primitive organic synthesis and especially to that of \(\alpha\)-amino acids (see Sect. 4.6.2). In addition to its role as a major source for early-Earth nitrogen chemistry, NO may also have served as an energy source for carbon–oxygen chemistry, which, however, could also be sustained by solar UV.

4.4.1 Endogenous \(\alpha\)-Amino Acids

It was the historic experiment of Miller (Miller 1953) that showed that \(\alpha\)-amino acids could have been formed on the primitive Earth from a reductive atmosphere. In the absence of reliable information on the composition of this atmosphere, the experiment was repeated on numerous occasions (Miller 1998) under different conditions, intended to simulate many of the different possible compositions \{\(\text{CH}_4, \text{NH}_3, \text{H}_2, \text{H}_2\text{O}\}\}, \{\(\text{CH}_4, \text{NH}_3, \text{H}_2\text{O}\}\}, \{\(\text{CH}_4, \text{H}_2, \text{N}_2, \text{NH}_3, \text{H}_2\text{O}\}\}, \{\(\text{CH}_4, \text{H}_2, \text{N}_2, \text{H}_2\text{O}\}\}, \{\text{CO}, \text{H}_2, \text{N}_2, \text{H}_2\text{O}\}\}, \{\text{CO}_2, \text{H}_2, \text{N}_2, \text{H}_2\text{O}\}\}, \text{under various } \text{H}_2/\text{CH}_4, \text{H}_2/\text{CO}\text{ or } \text{H}_2/\text{CO}_2\text{ ratios. The formation of amino acids was observed in all cases, even unfavourable ones (CO}_2, \text{H}_2, \text{N}_2, \text{H}_2\text{O}\), provided the H}_2/\text{CO}_2\text{ ratio was greater than 2, thus involving large amounts of hydrogen in the atmosphere}.\footnote{Recent observations show that the gases issuing from black smokers (undersea hot springs) contain considerable hydrogen amounts (Brack, lecture in Montpellier, 2002).} If we complement these atmospheric models by the sulphydryl function (–SH), phenylacetylene and indole (obtained by flash pyrolysis simulating the electrical discharges of gaseous \(\text{CH}_4, \text{NH}_3\) mixtures, see Miller 1998), we obtain...
17 protein α-amino acids, plus a collection of nonprotein amino acids analogous to those discovered in meteorites, together with some imino diacids.

As early as 1955, Stanley Miller showed that carbonyl derivatives, hydrocyanic acid and ammonia were the raw materials that produced these α-amino acids. He proposed the Strecker reaction as the formation mechanism of these compounds (Miller 1957, 1998). This proposition was used once again to explain the formation of some of the exogenous α-amino acids (see Sect. 4.3.2). It is remarkable to see how Miller’s proposition remains of current importance.

In addition to these synthetic pathways, others have been explored. We can cite:

- The one starting from HCN (Oró 1961) leading to low percentages of glycine and traces of alanine and aspartic acid.
- The one starting from 2-amino acrylonitrile H$_2$C=C(NH$_2$)CN (Ksander et al. 1987), which leads, in the absence of oxygen and water, to numerous organic compounds such as glutamic acid, and a precursor of the corrinoid cycle of vitamin B12 obtained with a very high yield (50%).

This last synthesis could have been prebiotic. The ease of synthesis of an essential building block of vitamin B12 interested Eschenmoser et al. (Ksander et al. 1987), who wondered whether the complexity of vitamin B12 was only apparent, and whether the selectivities of such syntheses starting from simple reagents might not be more common in the field of prebiotic chemistry than we had imagined. The authors suggested that research efforts should be developed in that direction.

We show in the next section of this chapter that the synthesis of N-carbamoyl amino acids could be a second example of selective prebiotic synthesis. To present these results, we first summarize the knowledge acquired through studying a multicomponent reaction system made up of the following molecules \{H$_2$O, HCN, R$^1$R$^2$CO, NH$_3$, R$^3$NH$_2$, R$^3$R$^4$NH, CO$_2$, B(OH)$_4^-$\}. Secondly, we use this knowledge to try to understand the formation dynamics of α-amino acids and N-carbamoyl amino acids on the primitive Earth.

4.5 Formation Mechanisms of α-Amino Acids and N-Carbamoyl Amino Acids
Via Strecker and Bücherer–Bergs reactions

The aim of this section is to present the reaction mechanisms of Strecker and Bücherer–Bergs reactions, involving 4 initial components \{H$_2$O, R$^1$R$^2$CO, HCN, NH$_3$\} and 5 initial components \{H$_2$O, R$^1$R$^2$CO, HCN, NH$_3$, CO$_2$\}, respectively.

We shall also examine extensions of these multicomponent systems, including borate$^4$B(OH)$_4^-$ (see Sect. 4.5.2), primary or secondary amines (R$^3$NH$_2$ or R$^3$R$^4$NH, respectively, see Sect. 4.5.3), the fate of both Strecker and Bücherer–Bergs reactions being different for each instance. Considering then the global
system made up of all 8 above components, the combination of Strecker and Bücherer–Bergs reactions together with those of borate will lead to a set of α-amino acids, N-carbamoyl amino acids, α-hydroxy acids and traces of imino diacids. The great structural diversity of several reactants: \(R^1R^2CO\), \(R^3NH_2\), \(R^3R^4NH\) (see Tables 4.1–4.5), will logically result in highly complex mixtures.

If such complexity is examined through combinatorial chemistry techniques only, we can get information on the set of final products only, losing the dynamic and mechanistic aspects such as equilibria and kinetics. This latter information, which is nonetheless indispensable for the understanding and modelling of dynamic processes, needs to be sought by means of more detailed, less global experimental approaches. That is the price to be paid for the quantitative study of chemical-evolution processes.

Our essential results are summarized in Commeyras et al., 2003. On this basis, and for the sake of clarity, the behaviour of the above 8-component system can be schematically presented as a first group of reversible steps producing a wide variety of chemical intermediates (Fig. 4.4), followed by a second group of irreversible steps resulting into a limited number of more stable species.

![Fig. 4.4. Reversible reactions and products (at equilibrium) of the 6-component system \(\{H_2O, HCN, R^1R^2CO, NH_3, CO_2, B(OH)_4^-\}\) ](image)

---

4 Boron is a non-negligible component of the Earth’s crust (0.03%), with borates involved in the composition of glass (13%). Therefore it may be worthwhile analyzing the potential participation of borates in organic molecules formation under both prebiotic and laboratory conditions, because of their catalytic role in some reactions.
Fig. 4.5. The set of (competing) irreversible reactions in the reaction network from the 6-component system \{H_2O, HCN, R^1R^2CO, NH_3, CO_2, B(OH)_4^-\}, showing pathways (A)–(E).
The special case of formaldehyde in the presence of high amounts of ammonia will not be examined however, since we considered it as too far from reasonable prebiotic conditions (see Sect. 4.6.2).

### 4.5.1 The Set of Reversible Reactions

We shall first examine the set of reversible reactions of the initial 6-component system \{H$_2$O, HCN, R$_1^3$R$_2^3$CO, NH$_3$, CO$_2$, B(OH)$_4^-$\} (additional constraints introduced by primary and secondary amines R$_3^3$NH$_2$ and R$_4^4$NH will be examined later). This set of reactions$^6$ (Fig. 4.4) is the starting point of Strecker and Bücherer–Bergs reactions that involve further, irreversible steps.

The reactions able to take place in this initial system (box on top of Fig. 4.4) mostly depend on the reactivity of the carbonyl derivatives R$_1^3$R$_2^3$CO. They can react:

- with water to give hydrates (not shown)
- with hydrocyanic acid to give cyanohydrins I (fast)$^7$
- with ammonia to give α-amino alcohols II

Amino alcohols II (slowly) lose an HO$^-$ anion to produce iminium cations III, which then react with the cyanide anion to give α-amino nitriles IV, the amine function of which reacts with carbonyl derivatives to produce α-amino dinitriles V. V are subject to two competitive reactions: either they lose an HO$^-$, yielding iminium cations VI, which further react with cyanide to produce α-amino nitriles IV, or V lose a proton to give alcoholate ions VIII.

CO$_2$ specifically reacts with α-amino nitriles IV to give carbanic acids IX that ionize into carbamates X. Boric acid B(OH)$_3$ (in equilibrium with borate B(OH)$_4^-$) specifically reacts with the cyanohydrins I to produce boric esters XI, which ionize into borates XII.

Under certain conditions (experimental but probably not prebiotic), the equilibria corresponding to these reversible reactions can be reached, thus constituting a reservoir of various nitrile families (cyanohydrins, amino nitriles, amino dinitriles, etc.). Their relative abundance depends on reactant structures (the nature of R$_1^3$, R$_2^3$), initial stoichiometry and concentration, and on the experimental conditions, especially pH, temperature and CO$_2$ pressure (Commeyras et al. 2003).

While such information is easily accessible experimentally, the main concern is then to determine whether this product distribution at equilibrium is representative or not of the final product distribution when further irreversible steps are.

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$^5$ This separation into two sets is made for the sake of clarity. Under prebiotic conditions, the equilibrium corresponding to the first set is very unlikely to be reached due to both reactant (e.g. ammonia) fluxes and competitive reactions from the second set.

$^6$ Equilibria of both hydration of carbonyl derivatives R$_1^3$R$_2^3$CO and carbonation of ammonia NH$_3$ (which are also part of this set) have been omitted to make Fig. 4.4 simpler.

$^7$ Molecular structures involved in Figs. 4.4–4.7 are labelled with bold Roman figures.
involved. In other words whether the final product distribution is under thermodynamic or kinetic control. This requires determination of kinetic data on both reversible and irreversible steps.

4.5.2 The Set of Irreversible Reactions

In these reaction media, irreversibility appears when nitriles (−CN) are transformed into amides (−CONH₂). Five different, competitive pathways (A–E, Fig. 4.5) can bring about this transformation⁸. Their starting points are the species I, IV, VIII, X, XII respectively, as shown in Fig. 4.4.

The first two pathways (A) and (B) are well known as the Strecker reaction⁹ (Strecker 1850; Miller 1957; see Sect. 4.3.2). They correspond to the intermolecular attack of the hydroxide anion (HO⁻) on the nitrile group of the cyanohydrins I and α-amino nitriles IV. They can explain the formation of both α-hydroxy amides XIIc and α-amino amides VIIIc, but not the formation of imino diacids VIIIb₃.

The other three reaction pathways (C), (D), (E) evidenced by us, result in the hydration of the nitrile group of I and IV in a more efficient way than both pathways (A) and (B). In addition, the reaction pathway (C) can explain the formation of imino diacids VIIIb₃.

The starting point of the pathway (C) is the alcoholate anions VIII. These anions react intramolecularly with their nitrile group, to give the α-amino amides VIIIc via two intermediates VIIIa and VIIIb. This pathway (C) leads to the same products as (B), but approximately 10⁵ times faster, through catalysis by carbonyl derivatives.

Concerning imino diacids VIIIb₃, Garrel (personal communication) recently showed that they originate from VIIIb. When the initial reagent concentrations are such as [R¹R²CO] > [CN⁻] ≫ [NH₃], the addition of cyanide to intermediates VIIIb occurs, that forms new nitriles VIIIb₁ as minor products, which then evolve into VIIIb₃. Therefore we consider that this reaction pathway (C) and its side-products must be completely included into the Strecker reaction, which should not be limited to reaction pathways (A) and (B).

The starting point of the pathway (D) is the carbamate anions X, which react intramolecularly with their nitrile group to give the hydantoins Xc via two intermediates Xa and Xb. This reaction is almost as fast as (C), and is known as the Bührer–Bergs reaction.

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⁸ An additional pathway to amino acids and involving hydrogen peroxide, was not taken into consideration because poorly compatible with prebiotic condition (Rossi et al. 1996).

⁹ The name “Strecker reaction” was initially given to the synthesis of α-amino acids by acidic hydrolysis (quenching of equilibrated aqueous alkaline) mixtures of carbonyl compounds, hydrocyanic acid and ammonia, referring to his original experiments. Later this name covered any experimental conditions using reaction pathways (A)+(B)+(C).
The starting point of the pathway (E) is the borate anions \( \text{XII} \), which react \textit{intra}molecularly with their nitrile group to give the \( \alpha \)-hydroxy amides \( \text{XIIc} \), regenerating, en route, the boric acid, which thus behaves as a catalyst in this reaction.

Kinetic studies enabled us to determine the kinetic laws and constants (4.6–4.10) of these reactions (Taillades et al. 1998; Commeyras et al. 2003), the following equations being valid in the pH 5–9 range, with values given at 25\(^\circ\)C:

\[
v_{(A)} = k_{(A)}[\text{HO}^-][\text{I}] \quad k_{(A)} = 3.8 \times 10^{-4} \text{L mol}^{-1} \text{s}^{-1} \quad (4.6)
\]

\[
v_{(B)} = k_{(B)}[\text{HO}^-][\text{IV}] \quad k_{(B)} = 1.4 \times 10^{-3} \text{L mol}^{-1} \text{s}^{-1} \quad (4.7)
\]

\[
v_{(C)} = k_{(C)}[\text{HO}^-][R^1R^2\text{CO}][\text{IV}] \quad k_{(C)} = 83 \text{L}^2 \text{mol}^{-2} \text{s}^{-1} \quad (4.8)
\]

\[
v_{(D)} = \frac{k_{(D)}}{1 + \frac{K_w}{K_1}}[\text{CO}_2][\text{IV}] \quad k_{(D)} = 1.2 \times 10^{-4} \text{L mol}^{-1} \text{s}^{-1} \quad (4.9)
\]

\[
v_{(E)} = k_{(E)}[\text{B(OH)}_3][\text{HO}^-][\text{I}] \quad k_{(E)} = 180 \text{L}^2 \text{mol}^{-2} \text{s}^{-1} \quad (4.10)
\]

with \( K_w \) and \( K_1 \) in (4.9) being the dissociation constants of water and of carbonic acid respectively (first dissociation), \( [\text{CO}_2]^\text{f} \) in (4.9) and \( [\text{B(OH)}_3]^\text{f} \) in (4.10) being the total concentration (acid + base forms) of carbonate + \( \text{CO}_2 \) and borate, respectively. It is noteworthy that above pH 7.5 the rate law (4.9) is independent of the pH. Further studies will be necessary to determine the temperature dependence of these rate constants.

In a first approach, however, at any pH between 5 and 9, and provided the concentration of either carbonyl compounds, carbonate or borate are above the millimolar range, the reaction pathways (A) and (B) (the only ones dealt with in previous prebiotic studies, see Sect. 4.3.2) should play a minor role comparatively to much faster pathways (C), (D), (E) using the same starting nitriles \( \text{I}, \text{IV}, \text{VIII} \). The latter pathways would thus be responsible for the formation of \( \alpha \)-amino amides \( \text{VIIIc} \), hydantoins \( \text{Xc} \), and \( \alpha \)-hydroxamides \( \text{XIIc} \). Nevertheless, such a conclusion must be adapted to prebiotic conditions, where the concentrations of the various nitrile families \( \text{I}, \text{IV}, \text{VIII} \) should be far from identical.

Studying the subsequent evolution of these \( \alpha \)-amino amides \( \text{VIIIc} \), hydantoin \( \text{Xc} \), and \( \alpha \)-hydroxamides \( \text{XIIc} \) into \( \alpha \)-amino acids \( \text{VIIId} \), \( N \)-carbamoyl amino acids \( \text{Xd} \) and \( \alpha \)-hydroxy acids \( \text{XIIId} \), respectively, showed that these three hydrolytic reactions have low but equivalent rates \((v_{(\text{CO}_2\text{H})} \approx 10^{-5}[\text{R} - \text{CONH}_2])\), see Commeyras et al. 2003). From this we can deduce that these reactions are incapable of modifying the selectivities induced by reactions (C), (D) and (E).
If the multicomponent system under consideration (Fig. 4.4) is completed with cyanate (the actual reacting species being cyanic acid HNCO), the system is driven to evolve towards N-carbamoyl amino acids (CAA) Xd through pathway (F). Kinetic studies of this reaction (Taillades et al. 2001) showed that the operating conditions required for carrying out this reaction are fully compatible with those of the other reactions described in Fig. 4.5. In addition, cyanic acid also reacts with amino amides VIIIc to give N-carbamoylamino amides.\textsuperscript{10} We observed (unpublished results) that the nitrosation of such compounds by gaseous NO\textsubscript{x} (see next chapter of this book) quantitatively yields hydantoins, the hydrolysis of which produces N-carbamoylamino acids.

Globally, we can thus conclude that:

The “multicomponent” system represented in Figs. 4.4 and 4.5 is kinetically controlled by irreversible reactions proceeding through reaction pathways (C), (D), (E).

This “multicomponent” system convergently evolves towards two families of compounds: α-hydroxy acids (minor) and N-carbamoyl amino acids (major).

4.5.3 Fate of Primary and Secondary Amines (R\textsubscript{3}NH\textsubscript{2}, R\textsubscript{3}R\textsubscript{4}NH)

Primary amines R\textsubscript{3}NH\textsubscript{2} follow the same reaction pathways as ammonia, with some limitations. Indeed while they can take pathways (B) and (C) to form α-NR\textsubscript{3}-amino acids VIIId, they are blocked on pathway (D) by the impossibility of forming isocyanates Xb, so that hydantoins Xc substituted on nitrogen-1 are inaccessible. A roundabout way to obtain such substituted hydantoins is to react cyanate with α-amino acids-NR\textsubscript{3} according to pathway (F), then to dehydrate the NR\textsubscript{3}-carbamoylamino acids Xd thus obtained. However, no such product has been identified in meteorites, which leads to the conclusion that these cyanates only played a minor role in the parent bodies, doubtlessly for kinetic reasons (see Sect. 4.7). This obviously does not exclude their having played a role on the primitive Earth. In the parent bodies, hydantoins could have been formed via the Bücherer–Bergs reaction.

The reactivity of secondary amines (R\textsubscript{3}R\textsubscript{4}NH) is even more severely limited. They can only lead to α-NR\textsubscript{3}R\textsubscript{4}-aminonitriles IV and then α-NR\textsubscript{3}R\textsubscript{4}-amino acids VIIId through pathway (B).

Taking these limitations into consideration provides interesting information in the analysis of prebiotic scenarios (see Sect. 4.6).

4.5.4 Conclusion

On the basis of the above chemical data, it is possible to explain the formation of imino diacids through Strecker processes, which therefore include the three pathways A, B, C allowing the initial multicomponent mixture {H\textsubscript{2}O, \textsuperscript{10}Cyanic acid reacts with amines in general; its reaction with ammonia produces urea (this simple reaction is not included in Fig. 4.5).
HCN, R₁R₂CO, R³R⁴NH, CO₂, B(OH)₄⁻ to be driven out of equilibrium. The Bücherer–Bergs reaction is a fourth pathway D allowing this equilibrium to be broken, and leading to CAA. The kinetics of pathways C, D, E that predominate over A and B determine the relative hydroxy acid/amino acid/CAA formation ratio. The presence of cyanic acid may have convergently driven AA evolution towards CAA, which would then become the most abundant products of this chemical process.

In the next section we examine possible prebiotic implications of such chemistry.

4.6 Prebiotic Formation of α-Amino Amides and Hydantoins Through Strecker and Bücherer–Bergs Reactions

Dynamic study of complex systems generally provides information about the preferential directions taken by the system under the pressure of a given environment. In the case of chemical evolution, these studies enable us to imagine how the molecular complexification operated, and what were the most probable mechanisms for this complexification.

4.6.1 Formation of Exogenous α-Amino Amides and Hydantoins

4.6.1.1 Environment and Reagents

Both Strecker and Bücherer–Bergs reactions require the presence of (rather liquid) water, which puts constraints on the places where they might have occurred. Exogenous organic matter delivered by meteorites is considered to have been formed in parent bodies, the history of which indicates that they could have met temperature ranges of ca. 263–298K (Clayton and Mayeda 1984), with the possible presence of (interstitial or permafrost) liquid water.¹¹

The analysis of meteorite extracts led Peltzer et al. (1984) to propose the Strecker reaction to explain the formation of α-amino acids in parent bodies. The presence of α-hydroxy acids and (recently discovered) of imino diacids (Pizzarello and Cooper, 2001) strongly confirm this hypothesis. Besides, investigation by Lerner (1997) on the Strecker reaction in aqueous solution simulating the putative parent-body composition ([NH₃] = 2 mM, [CN] = 5 mM, [aldehydes] = 7 mM, [ketones] = 0.75 mM) at various temperatures (263 and 295K), shows the formation of the 3 components of the Miller–Strecker signature (α-hydroxy- and α-amino acids, imino diacids) after a 4-month reaction. When the reaction was performed at 295K, only the compounds

¹¹ The synthesis of amino acids and related compounds in interstellar molecular clouds is also probable; however, the preservation of such organics from presolar origin during accretion of the (hot) protoplanetary disc is very doubtful.
deriving from aldehydes were observed, whereas at 263K derivatives from both aldehydes and ketones were observed. The formation of these imino diacids appeared not to be influenced by the presence of meteoritic minerals.

From these data we can reasonably consider that meteoritic amino acids were synthesised in parent bodies through the Strecker reaction. We can add that the temperature was probably lower than 263K (considering the abundance of α-alkyl, α-amino acids in meteorites), and that the ammonia concentration was quite low compared to that of other reagents such as HCN or carbonyl compounds.

We must, however, take care on requirements put on the prebiotic environment to fit the Strecker reaction with meteorite amino acids, since their analysis through extraction processes gives merely an estimation of meteorite content that can easily be modified by the extraction process itself.

### 4.6.1.2 Suitability of Reactions to Prebiotic Conditions

We have seen that reaction pathway (C) is catalyzed by carbonyl derivatives. When the catalyst used is formaldehyde, the activation energy of this reaction is zero (Pascal et al. 1980; Commeyras et al. 2003). Such low activation energy values are generally the consequence of favoured intramolecular reactions, as it is the case of the hydration of nitriles by alcoholate anions VIII in pathway (C). Noteworthy that the rate constant for this reaction ($k_{\text{H}_2\text{CO}} = 3.4 \times 10^7 \text{L}^2\text{mol}^{-2}\text{min}^{-1}$) is of the same magnitude order as enzymatic reaction rate constants. Current research into the emergence of the catalytic activities of enzymes makes reference to such reactions (Pascal 2003).

A similar cyclization of carbamates X occurs in pathway (D), for which the (yet unknown) activation energy is probably quite low, thus allowing the reaction to occur at low temperatures. However, this step is probably not the rate-determining one for hydantoin Xc formation, which might rather be the opening of Xa with formation of isocyanate Xb (requiring base catalysis). Further investigation is necessary to confirm this hypothesis.

Conversely to (D) and similarly to (C), the (fast) cyclisation of XII in pathway (E) is probably the rate-determining step in borate-catalysed formation of α-hydroxyamides XIIc. However, there is no information about the concentration of borate in prebiotic media.

The above examples of intramolecular catalysis are certainly not unique in prebiotic chemistry; they could justify continuing research in this direction, especially since they have already led to the development of energy-economical, waste-free industrial processes (Commeyras et al. 1976; Taillades et al. 1986).

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12 We explain this by the higher thermolability of tertiary α-amino nitriles (ketone derivatives) compared to that of secondary α-amino nitriles (aldehyde derivatives), the former thus being unable to react with carbonyl compounds (pathway C on Fig. 4.5) at higher temperature to form the α-alkyl amino amides and acids (Commeyras et al. 2003).
4.6.2 Endogenous Formation of α-Amino Amides and Hydantoins

To try to explain the formation of endogenous α-amino acids it is obviously desirable to have information about the nature and concentrations of the species present on the primitive Earth, and about the pH and temperature of the oceans. This knowledge is still imprecise and can thus only lead to hypotheses.

4.6.2.1 Availability of Starting Compounds

The evaluation range for the partial pressure of CO$_2$ is very wide, going from $10^{-4}$ bar (Pinto et al. 1980) to more likely estimates, ranging between 0.1 and 10 bar (Owen et al. 1979; Kasting and Ackerman 1986; Mojzsis et al. 1999).

While the formation of carbonyl derivatives and cyanide does not seem to be problematic, evaluation of their relative and especially absolute concentrations remains highly uncertain. Values of $2 \times 10^{-2}$ mol L$^{-1}$ for these different constituents (Pinto et al. 1980) have been proposed. To our knowledge, these estimations have not been updated.

Concerning ammonia, its origins and concentration have been the subject of numerous investigations. The initial proposition, that it was formed by reduction of nitrogen by atmospheric hydrogen ($\text{N}_2 + 3 \text{H}_2 \rightarrow 2 \text{NH}_3$) (Bada and Miller 1968), has been contested. Two other reactions have been proposed. The first is based on hydrolysis of cyanic acid ($\text{HNCO} + \text{H}_2\text{O} \rightarrow \text{NH}_3 + \text{CO}_2$), itself formed by electrical discharges in a hypothetical primitive atmosphere made up of $\text{N}_2$, CO$_2$ and H$_2$, (Yamagata and Mohri 1982). The other involves reduction of NO by Fe$^{2+}$, which was common in the primitive ocean (Summers and Chang 1993, Summers 1999). The formation of NO in considerable quantities (Prinn and Fegley 1987; Navarro-Gonzalez et al. 1998, 2001) could thus have led to regular and sufficient production of NH$_3$, a requirement for the production of amino acids. If, however, we take into account the fact that NH$_3$ readily photolyzes, it is likely that the ammonia concentration in the primitive atmosphere was still very low. Summers (1999) estimated the (pH dependent) steady-state concentration of ammonia (both NH$_3$ and NH$_4^+$) in primitive Earth oceans to have remained within the $2 \times 10^{-7}$ mol L$^{-1}$ (pH 8.5) to $3 \times 10^{-5}$ mol L$^{-1}$ (pH 5) limits. These very low concentrations led these authors to doubt the efficiency of the Strecker process, although afterwards, being unable to find an alternative, they accepted it as probable.

These facts must therefore be taken into consideration when examining the endogenous synthesis of α-amino acids.

4.6.2.2 Thermodynamic Aspects

From a thermodynamic point of view, taking into account these low reactant concentrations and the equilibrium constants $K_{\text{cya}}$ and $K_{\text{an}}$ associated to the reactions forming cyanohydrins I and α-amino nitriles IV respectively, it is easy
to estimate their relative concentration. In the case of formaldehyde, $K_{\text{cya}} = 4.76 \times 10^3 \text{L.mol}^{-1}$ and $K_{\text{an}} = 4 \times 10^7 \text{L}^2 \text{mol}^{-2}$, therefore at equilibrium the concentration ratio of $\text{I}$ to $\text{IV}$ would be of the order of 1000/1. Nevertheless, the situation is different due to the fact that the relative concentrations of these two products is determined by their formation rates (kinetic control) and not by their relative stability (thermodynamic control).

### 4.6.2.3 Kinetic Aspects

From a kinetic point of view, cyanohydrins are formed within a few minutes ($t_{1/2} = 1 \text{min at any pH}$) whereas $\alpha$-amino nitriles are formed much more slowly ($t_{1/2} = 6 \text{h, maximum rate at pH 9}$). As soon as formed, $\alpha$-amino nitriles $\text{IV}$ react, partly decomposing back to initial reactants (with a pH-dependent rate, maximum above pH 5–6) and partly hydrating into $\alpha$-amino amides $\text{VIIIc}$ via the irreversible reaction (C). We have shown that this hydration reaction (C) is 10 times faster than the decomposition reaction (Pascal et al. 1978; Commeyras et al. 2003). The consequence (Fig. 4.6) is that the formation equilibria of the $\alpha$-amino nitriles $\text{IV}$ should never be attained under prebiotic conditions, because these compounds $\text{IV}$ are immediately and irreversibly transformed into $\alpha$-amino amides. We can add that the B"ucherer–Bergs reaction (D), leading to the hydantoins $\text{Xc}$, should have amplified this process of withdrawing $\alpha$-amino nitriles from the reversible reaction system.

Therefore even for ammonia concentrations of $10^{-6} \text{mol L}^{-1}$, equilibrium shifts towards amino amides and hydantoins may have allowed the major formation of these compounds to the detriment of hydroxy amides. Then the summary of thermodynamic and kinetic data seems in agreement with: (1) a similar abundance of amino acids compared to hydroxy acids in meteorites, and (2) the fact that compounds originating from irreversible reactions of $\alpha$-amino nitriles ($\alpha$-amino amides, hydantoins) might have formed more abundantly on the primitive Earth in presence of carbonyl derivatives and ammonia (in lower concentration), if the pH of primitive oceans was around 5–6.

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Fig. 4.6. Rapid and irreversible reaction of $\alpha$-amino nitriles through pathways (C) and (D) does not enable the formation equilibrium of $\alpha$-amino nitriles to be established

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Cyanohydrins ($\alpha$-hydroxy nitriles) $\text{I}$ are stable in aqueous solution, unlike carbonyl derivatives or hydrocyanic acid. We can thus state that they protected both carbonyl derivatives and hydrocyanic acid against degradation, enabling these compounds to wait for the gradual arrival of ammonia.
In summary, it is reasonable to conclude that the formation rates of α-amino amides and hydantoins on the primitive Earth, via the Strecker and Bücherer–Bergs reactions, could have been controlled by the formation rate of ammonia.

4.7 Convergent Evolution Towards N-Carbamoyl Amino Acids under Prebiotic Conditions

On the primitive Earth, even when controlled by the ammonia formation rate, a “multicomponent” system represented by Figs. 4.4 and 4.5 could only have spontaneously evolved (Fig. 4.7) into the three families of compounds analyzed above (see Sect. 4.5.2), i.e. a minority of α-hydroxy amides XIIc (omitted in Fig. 4.7), and a majority of α-amino amides VIIlc and hydantoins Xc. The subsequent evolution of these compounds into α-hydroxy acids XIId, α-amino acids VIIIId and N-carbamoyl amino acids Xd with equivalent reaction rates ($3.6 \times 10^{-5}\text{h}^{-1}$ and $2.2 \times 10^{-5}\text{h}^{-1}$ measured at pH 8 and 25°C, see Commeyras et al. 2003) cannot have influenced the selectivity generated by the fast steps (C) (D) (E) investigated above.

Concerning the N-carbamoylation reaction, it most certainly played an important prebiotic role\(^\text{14}\), but it can only have been involved in the slow step

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\(^{14}\) The estimated pH of the primitive ocean (5–7) (Mojzsis et al. 1999) is favorable to carbamoylation reactions. Cyanic acid HNCO is formed in model gas mixtures of
(\(k(F) \approx 1.7 \times 10^{-3}\ \text{L}\ \text{mol}^{-1}\ \text{s}^{-1}\) at 50°C and pH 6.5) (Taillades et al. 2001; Commeiras et al. 2003), considerably later than the preceding fast steps which controlled selectivity.\(^{15}\)

It is therefore reasonable to consider cyanate (in equilibrium with cyanic acid) in the primitive ocean at pH 5–7, to have slowly transformed \(\alpha\)-amino amides \(\text{VIIIc}\) and \(\alpha\)-amino acids \(\text{VIIId}\) into \(N\)-carbamoyl amino acids \(\text{Xd}\) by two different pathways: either via \(N\)-carbamoyl amino amides and hydantoins, or directly from \(\alpha\)-amino acids (Fig. 4.7).

The case of meteorites, where amino acids would be more abundant than both hydantoins and (yet unobserved) \(N\)-carbamoyl amino acids, appears contradictory with a convergent \(N\)-carbamoyl amino acid synthesis. Although the measured ratio may be biased from the original meteorite composition (by e.g. impact or extraction processes), this is probably rather due to quite different conditions having occurred in parent bodies comparatively to the primitive Earth, especially concerning CO\(_2\) and cyanic acid abundance. Further analytic and chemical investigations should be able to provide useful information on these parent-body conditions.

In summary, on the primitive Earth, the set of reaction processes Fig. 4.7 could have converged not towards free \(\alpha\)-amino acids \(\text{VIIId}\), but rather towards \(N\)-carbamoyl amino acids \(\text{Xd}\). In the next chapter we shall examine how these \(N\)-carbamoyl amino acids could have led to peptides.

4.8 Conclusions

In this chapter, we have shown that the multicomponent system \(\{H_2O, HCN, R^1R^2CO, NH_3, R^3NH_2, R^3R^4NH, CO_2, B(OH)_4^-\}\) could have been the origin of the \(\alpha\)-amino acids and derivatives discovered in meteorites and formed on the primitive Earth.

The formation mechanisms of these derivatives have been exhaustively examined, and the Strecker and Bücherer–Bergs reactions can be said to have played a major, even unique, role in the formation of these compounds. It was these reactions that led the above multi-component system, made up of essential prebiotic molecules, to evolve quickly, majoritarily and selectively into \(\alpha\)-amino acids and \(N\)-carbamoyl amino acids.

Under prebiotic conditions, the formation rates of these compounds could have been controlled by the ammonia formation rate.

The involvement of cyanic acid, an essential prebiotic molecule, in addition to the above reactions, in a subsequent slower step, could have led to \(N\)-carbamoyl amino acids alone.\(^{15}\)

\(^{15}\) This additional example confirms (were it still necessary) the absolute necessity of studying the dynamics of potentially prebiotic systems in order to understand their chemical evolution.
The knowledge acquired about these reactions enables us to envisage kinetic modelling of the whole system, the only possible way to understand the respective contributions of all the forces involved.

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